E3 Contd

hydrochloride, verapamil hydrochloride, propoxyphene hydrochloride, hydrocodeine bitartrate, acyclovir sodium, albuterol sulfate, ampicillin sodium, benztropine mesylate, benzphetamine hydrochloride, bupivacaine hydrochloride, bupropin hydrochloride, clorphenamine maleate and chlorpromazine hydrochloride.

REMARKS

Claims 1-24, 26, 30 and 33-38 are in the application.

Claims 1-24, 26, 30 and 33-38 stand rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claims 1-7, 9, 10, 12, 13, 17-24, 26 and 33-38 stand rejected under 35 USC 102(b) as being anticipated by Akkerboom et al, U.S. Patent 5 211 958.

Claims 1-24, 26, 30 and 33-38 stand rejected under 35 USC 103(a) as being unpatentable over Weintraub et al, U.S. Patent 4 013 785.

The Information Disclosure Statement stands objected to on the grounds that it fails to comply with 37 CFR 1.98(a)(2).

THE REJECTION OF CLAIMS 1-24, 26, 30 AND 33-38 UNDER 35 USC 112, SECOND PARAGRAPH

In making this rejection, the Examiner states:

"The term "fairly, "highly," "fairly rapidly," and the limitation "rapidly precipitate out of the solution" in claim 1 and 35 are relative and render the claim indefinite. The term "fairly," "highly," and the limitations "rapidly precipitate out of the solution" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Moreover, such terms are not art recognized terms (see Remington, page 195, table 1). Thus, the metes and bounds of the claims are not clear."

While the Examiner has correctly noted that the term "poorly soluble", "fairly soluble" and "highly soluble" are relative terms, he apparently does not appreciate that these terms were chosen to indicate that the fairly soluble or highly soluble compound defined in Claim 1 is higher in solubility relative to its poorly soluble parent free base or free acid drug. Remington's definition was not specifically used so that the claims could be most clearly understood.

With respect to the Examiner's statement that the specification does not contain a standard for determining the relative meaning of "poorly soluble", "fairly soluble", and "highly soluble", the Examiner's attention is directed to page 3, lines 10-20, of the specification, wherein it is stated:

> "A rapidly precipitating drug is a pharmaceutical compound, or its salt form, which when introduced in water, or simulated physiological fluids at body temperature, begins to dissolve fairly rapidly and then begins to rapidly precipitate out of solution within 60 min to a less soluble form which provides a concentration that is less than therapeutic. This precipitation results in slow and incomplete dissolution. In most cases, the amount precipitating can be up to 90% or greater which leave about 10% or less available for therapeutic activity. It is preferred that the rapidly precipitating drug is a fairly soluble or highly soluble salt form of a poorly soluble free base or free acid drug or an anhydrous form of a poorly soluble free base or free acid drug. The rapidly precipitating drugs are prone to supersaturation as is known to those skilled in the art."

This description provides a clear objective standard in terms of relative solubility, that is, the more soluble compound (typically a salt of the type used to increase solubility). Specifically, in the most preferred case [which is prone to most critical precipitation], the solubility of the higher soluble compound (e.g. salt or anhydrous form) would be roughly at least 100 times more soluble than the hydrated form of the parent free base or free acid. As a consequence thereof, greater than 90% of a drug meeting the criteria

precipitates within the 60 minute time frame as described in the case. In this regard, see the enclosed Declaration Under 37 CFR 1.132 of Dr. Alice C. Martino, pages 1-3, under the heading "STANDARD FOR ASCERTAINING THE SCOPE OF THE INVENTION", where this characteristic of a rapidly precipitating drug is described.

Claim 1 further adds definition to the nature of the "rapidly precipitating drug" by reciting that the drug is prone to supersaturation when introduced in water, or simulated fluids at body temperature. Hence, one skilled in the art could determine whether a particular drug form is encompassed by the claim by subjecting it to in vitro tests well known in the art to determine if the drug form (1) is a more soluble form of its hydrated parent moiety, (2) will rapidly dissolve in water to form a saturated solution and (3) precipitate (90%) out within 60 minutes of forming the saturated solution. This determination can be made without undue experimentation.

Claims 2-24, 26, 30 and 33-38 are not indefinite for the reasons that Claim 1 is not indefinite. Claim 38 recites specific "fairly soluble" or "highly soluble" drugs, so this is an additional reason that Claim 38 is not indefinite.

THE REJECTION OF CLAIMS
1-7, 9, 10, 12, 13, 17-24, 26 AND 33-38
UNDER USC 102(b) AS BEING ANTICIPATED BY
AKKERBOOM ET AL, U.S. PATENT 5 211 958

Akkerboom et al does not anticipate Claims 1-7, 9, 10, 12, 13, 17-24, 26 and 33-38 and therefore said claims are patentably distinguishable thereover.

Claim 1 as presently amended is directed to a non-sustained release, non-chewable tablet composition which comprises a rapidly precipitating drug, and only a rapidly precipitating drug as the pharmaceutically active ingredient, in an amount from about 5 to about 60% and at least one member

selected from the group consisting of a binder in an amount of from about 2 to about 25% and a superdisintegrant in an amount from about 6 to about 40%; (a) wherein the rapidly precipitating drug is a fairly soluble or highly soluble salt form of a poorly soluble free base or free acid or anhydrous form of a poorly soluble free base or free acid that is prone to supersaturation when introduced in water or simulated physiological fluids at room temperature, and (b) wherein more than 90% of the rapidly precipitating drug precipitates out within 60 minutes after coming into contact with water or simulated physiological fluids at body temperature, with the proviso that the rapidly precipitating drug is not delavirdine mesylate. The recitation "and only a rapidly precipitating drug as the pharmaceutically active ingredient" does not constitute new matter because the specification fully supports tablet formulations that contain "a rapidly precipitating drug" as the only active ingredient. Further limitations can be added to a claim to define over prior art without adding new matter or failing to comply with the written description requirement.

Claim 1 defines a tablet formulation that produces a supersaturated state, i.e., a higher solution concentration of a drug salt in solution, upon dissolution of a tablet that is prepared with soluble salts of poorly soluble drugs. In addition to the use of a more soluble drug, another inventive feature is that this resulting supersaturated state is maintained for a longer period of time by HPMC or other binders. The advantage of the supersaturated state and its maintenance for a longer period of time is that the higher and prolonged drug concentration in solution in the GI tract results in faster absorption and improved oral bioavailability.

For a reference to anticipate the claim, it must disclose each and every limitation of the claim. Akkerboom et al fails to disclose a number of the limitations of Claim 1. Claim 1

requires that the drug be either (a) a more soluble salt of a poorly soluble acidic or basic drug or (b) a more soluble anhydrous form of a poorly soluble hydratable acid or base as a basic drug.

The various tetracycline hydrates disclosed by Akkerboom et al are not salts. A hydrate is not a salt of a compound. See Declaration of Dr. Martino, page 4, third and fourth paragraphs under the heading "ANTICIPATION BY AKKERBOOM ET AL U.S. PATENT 5 211 958". These hydrates will not generate a supersaturated state in water or simulated physiological fluids at body temperature.

Calcium chlortetracycline, referred to by Akkerboom et al as a salt, is a chelate. This, calcium chlortetracycline does not meet the "rapidly precipitating" requirement of Claim 1 because it is neither a more soluble salt of a poorly soluble drug or a more soluble anhydrous form of a poorly soluble free acid or base. See Dr. Martino's Declaration, page 4, paragraph bridging pages 4 and 5.

The Examiner asserts in the last line on page 3 of the Office Action:

> "In another word, the tetracycline trihydrate used by Akkerboom, is more soluble that (than) its respective tetracycline free base or anhydrous form."

However, there is no evidence of record in support of this assertion and it is rebutted by Dr. Martino. See Dr. Martino's Declaration, page 4, fifth paragraph.

The Examiner further states in the last sentence of the third paragraph on page 3 of the Office Action that:

> "Further, Applicant has not provided any evidence showing that the "low soluble drugs" of Akkerboom do not encompass "the instant fairly soluble drug."

In making this statement, the Examiner overlooks the fact that the present claims specifically exclude the hydrated tetracyclines that are suitable for use in the Akkerboom et al tablet by requiring that if a free acid or free base is used

as the rapidly precipitating drug, the free acid or base has to be anhydrous.

THE REJECTION OF CLAIMS 1-24, 26, 30 AND 33-38 UNDER 35 USC 103(a) AS BEING UNPATENTABLE OVER WEINTRAUB ET AL, U.S. PATENT 4 013 785

The present claims 1-24, 26, 30 and 33-38 are patentably distinguishable over Weintraub et al. Weintraub et al discloses an n-acetyl-p-aminopehnol (APAP) tablet that contains fumed silica and a process for manufacturing the same. APAP is not a rapidly precipitating drug. See Dr. Martino's Declaration, page 5, second paragraph under the heading "UNOBVIOUSNESS OVER WEINTRAUB ET AL U.S. PATENT 4 013 785", lines 12-13.

While it is disclosed that the tablet may contain active agents in addition to APAP, the disclosed tablet requires the presence of APAP. Present Claims 1-24, 26, 30 and 33-38 exclude the presence of APAP in the tablet composition defined therein by reciting that the fast precipitating drug is the only active pharmaceutical ingredient in the composition. There is nothing in Weintraub et al that either teaches or suggests a tablet that does not contain APAP. Therefore, Weintraub et al does not render Applicants' claims obvious. Furthermore, Claim 35 requires that the claimed tablet composition be prepared without using heating, solvent or grinding, all of which are required in the preparation of the Weintraub et al tablet.

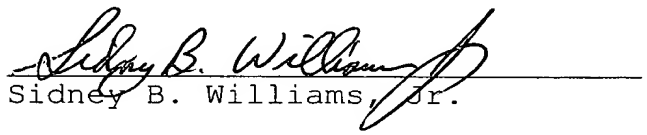
THE OBJECTION TO THE INFORMATION DISCLOSURE STATEMENT

The Examiner indicates that the Information Disclosure Statement (IDS) submitted fails to include copies of items AH-AR and that he was unable to locate them in the parent application. A review of the client's parent application file reveals an IDS that was attached to a Notice of Allowability

issued in the parent case. The references AH-AR are included in that IDS and they were initialed by the Examiner. Copies of that Notice of Allowability and the attached IDS are enclosed.

In view of the amendments/arguments presented above and Dr. Martino's Declaration, withdrawal of the rejection of the claims and objection to the IDS, and expeditious passage of this case to issue, are respectfully solicited.

Respectfully submitted,



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Encl: Marked-Up Amended Claims
Declaration Under 37 CFR 1.132 of Dr. Alice C. Martino, with Exhibits 1, 2 and 3
Notice of Allowability and IDS from Parent Case (6 pages)

136.0112

IN THE CLAIMS

Please amend Claims 1, 35 and 38 as follows.

1. (~~Twice~~Three Times Amended) A non-sustained release, non-chewable tablet composition which comprises~~:~~ a rapidly precipitating drug, and only a rapidly precipitating drug as the active pharmaceutical ingredient, in an amount from about 5 to ~~about~~ 60% and at least one member selected from the group consisting of a binder in an amount of from about 2 to about 25% and a superdisintegrant in an amount from about 6 to about 40%; (a) wherein the rapidly precipitating drug is a fairly soluble or highly soluble salt form of a poorly soluble free base or free acid or an anhydrous form of a poorly soluble free base or free acid that is prone to supersaturation when introduced in water, or simulated physiological fluids at body temperature, begins to dissolve fairly rapidly and then begins to rapidly precipitate out of solution and (b) wherein more than 90% of the rapidly precipitating drug precipitates out within 60 minutes after coming into contact with said water or simulated physiological fluids at body temperature, with the proviso that the rapidly precipitating drug is not delavirdine mesylate.

35. (~~New~~Amended) A non-sustained release, non-chewable tablet composition which comprises a rapidly precipitating drug, and only a rapidly precipitating drug as the active pharmaceutical ingredient, in an amount from about 5 to 60%, and at least one member selected from the group consisting of a binder in an amount of from about 2 to about 25% and a superdisintegrant in an amount from about 6 to about 40%, wherein (a) the rapidly precipitating drug is a fairly soluble or highly soluble

salt form of a poorly soluble free base or free acid or an anhydrous form of a poorly soluble free base or free acid that is prone to supersaturation ~~pharmaceutical compound, or its salt form, which~~ when introduced in water, or simulated physiological fluids at body temperature, begins to dissolve fairly rapidly and then begins to rapidly precipitate out of solution and (b) wherein more than 90% of the rapidly precipitating drug precipitates out within 60 minutes after coming into contact with said water or simulated physiological fluids at body temperature; ~~to a less soluble form which provides a concentration that is less than therapeutic,~~ and wherein the rapidly precipitating drug, microcrystalline cellulose, binder and superdisintegrant are mixed in and compressed into a tablet without heating, solvent or grinding, with the proviso that the rapidly precipitating drug is not delavirdine mesylate.

38. (~~New~~Amended) A composition according to Claim 1, wherein the drug is selected from ~~pseudoephedrine,~~ clindamycin hydrochloride, cloridine hydrochloride, diphenhydramine hydrochloride, fluphenazine hydrochloride, hydromorphone hydrochloride, naloxone hydrochloride, oxytetracycline hydrochloride, phenylephrine hydrochloride, pheniramine maleate, tetracycline hydrochloride, verapamil hydrochloride, propoxyphene hydrochloride, hydrocodeine bitartrate, acyclovir sodium, albuterol sulfate, ampicillin sodium, benztropine mesylate, benzphetamine hydrochloride, bupivacaine hydrochloride, bupropin hydrochloride, clorphenamine maleate and chlorpromazine hydrochloride.